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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,846	12/04/2001	Sanne Moller Knudsen	6236.200-US	6436

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,846	KNUDSEN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43,46 and 47* is/are pending in the application.

4a) Of the above claim(s) *46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-43,46 and 47* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/07/02, 10/09/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed 12/04/01 has been entered.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-43, drawn to method of identifying a compound interacting with a G protein-coupled receptor, classified in class 435, subclass 7.2.

II. Claims 46-47, drawn to method of producing a pharmaceutical preparation, classification dependent on compound structure, for example, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as in that both use the method of identifying a GPCR interacting compound, but because II requires a compound instead of simply an assay. the inventions are distinct. The invention of Group I does not require the particulars of the Group II as claimed for patentability, and the method of making the pharmaceutical preparation could have utility by itself as an effector of a GPCR.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification and each invention requires a separate non-coextensive search, restriction for examination purposes as indicated is proper.

During a telephone conversation with Dr. Reza Green on February 17, 2004, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-43. Affirmation of this election must be made by applicant in replying to this Office action. Claims 46-47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because of the following informalities: on page 22, line 7, "GPCR/BHK cells?/".

Appropriate correction is required.

Claim Objections

Claim 4 is objected to because of the following informalities: a hyphen is present in "phosphorylation-independent" in line 4, but does not occur elsewhere in claims (*e.g.*, claim 13 or 25). Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 9, 10-12, 18, 22-24, 31-33 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,891,646 (cited by Applicants).

US Patent 5,891,646 (Barak et al., '646) teaches a method of identifying compounds capable of initiating signaling of or deactivating a GPCR (β2adrenergic receptor) by contacting HEK cell membranes comprising the GPCR with βarrestin2-GFP, visually separating GPCR-bound and -unbound arrestin, and determining the level of GPCR-bound arrestin. The test compound, isoproterenol, acted as an agonist, mediating an increase in the bound compared to unbound arrestin as was seen by enhanced membrane arrestin fluorescence with concomitant loss of cytosolic fluorescence, such that the arrestin distribution shifted to the membrane. Agonist exposure caused an increase of ten-fold compared to control (distribution prior to agonist exposure) (col. 19. lines 48-63). The same experiment was conducted with the GPCR antagonist propanol (*e.g.*, col. 20, lines 19-30) with the opposite results, *i.e.*, more unbound than bound was seen. '646 is silent with respect to kinase presence; however, because wildtype arrestin will not bind unphosphorylated GPCR (*e.g.*, col. 1, lines 40-42) and phosphorylation requires a kinase,

the kinase was necessarily present in the cell. Also taught is the method with addition of GRK kinase (col. 9, lines 38-42 and Fig. 5). The same method was conducted with an added carrier, mouse monoclonal antibody directed against an 12CA5(HA) tag of the $\beta_2$adrenergic receptor, which bound the cell membrane indirectly through binding of the membrane-associated translocated GPCR (col. 20, lines 50-62).

Note that because the claims are drawn to a method "comprising" and because the cell membrane of part (a) of the instant claims is not necessarily isolated, the instant invention reads on using whole cells.

Claims 1-19, 22-40 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Kovoor et al. (J. Biol. Chem., 274(11):6831, 1999, cited by Applicants).

Kovoor et al. teach a method of identifying a compound capable of initiating signaling of or deactivating a GPCR by contacting membranes (liposomes) containing $\beta_2$adrenergic receptor (βAR) phosphorylated by a GRK (also known as βARK) with wildtype arrestin or R169E or 1-382 arrestin mutants. The arrestin was labeled with tritium, and that which bound a Sepharose column and to receptor-containing membranes was separated and quantified by liquid scintillation (legend of Fig. 1). The compound tested was isoproterenol.

Note that the method is the same for identifying an agonist or antagonist, and determination of whether the test compound is an agonist or antagonist by looking at levels is a mental step.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4-8, 11, 13-17, 23, 25-29, 32 and 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,891,646 and further in view of Kovoor et al. (J. Biol. Chem., 274(11):6831, 1999) and Palczewski (Eur. J. Biochem., 248:261-269, 1997).

US Patent 5,891,646 is relied upon for the teaches above. US Patent 5,891,646 does not teach a phosphorylation-independent arrestin mutant or, specifically, GRK.

Kovoor et al. teach two phosphorylation independent βarrestin mutants: one which is R169E and another with position 383 being a stop codon so that it comprises 1-382. These arrestins are constitutively active and *in vitro* bind the agonist activated $\beta_2$adrenergic receptor regardless of its phosphorylation status. They also bind δ opiod receptor. Also taught is the model for signaling by diverse GPCRs (p. 6831, beginning last sentence of col. 1). "According to the model, activated receptor is first phosphorylated by a G protein-coupled receptor kinase (GRK). An arrestin protein binds to the activated phosphoreceptor, thereby blocking G protein interaction...," forming an "arrestin-receptor complex". The discussion of effector molecules (col. 2, beginning middle of first paragraph) says there are only six mammalian GRKs and four arrestins that have been found so far. "This suggests that at least some of the kinases and arrestins regulate numerous receptors. Thus, these proteins are attractive targets for research designed to delineate common molecular mechanisms underlying the regulation of GPCR signaling in cells (and to create fairly universal tools for the experimental and/or therapeutic intervention in the process)."

It would have been obvious at the time the invention was made to practice the assay of '646 with a phosphorylation-independent arrestin mutant taught by Kovoor et al. to avoid the need of a kinase and because Kovoor teaches that "...these proteins [*i.e.*, arrestins] are attractive targets for research designed to delineate common molecular mechanisms underlying the regulation of GPCR signaling in cells...." Further, even if '646 did not use a GRK, one would have been motivated to use a GRK because Kovoor et al. teach that GRKs are responsible for phosphorylating GPCRs so that arrestins can bind.

Claims 19-21 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kovoor et al. (J. Biol. Chem., 274(11):6831, 1999) and US Patent 5,670,360 (Thorens).

Kovoor et al. teach a method of identifying a compound capable of initiating signaling of or deactivating a GPCR by contacting membranes (liposomes) containing $\beta_2$adrenergic receptor (β_2AR) phosphorylated by a GRK (also known as βARK) with wildtype arrestin or R169E or 1-382 arrestin mutants. The arrestin was labeled with tritium, and the arrestin which bound to a Sepharose column and to receptor-containing membranes was separated and quantified by liquid scintillation (legend of Fig. 1). The compound tested was isoproterenol. Also taught is recombinant expression of β_2AR and opiod receptor GPCRs in *Xenopus* oocytes (p. 6832, col. 1, beginning of first paragraph). Kovoor does not teach using SPA (scintillation proximity assay) beads or WGA (wheatgerm agglutinin).

US Patent 5,670,360 ('360) teaches an assay to identify a compound capable of activating or deactivating the GPRC GLP-1 receptor by means of a high throughput screening assay using SPA (scintillation proximity assay) beads coated with WGA (wheatgerm agglutinin). The WGA allowed GPL1- receptor bearing membranes to be immobilized on SPA beads. The membranes were prepared by recombinant cloning of the receptor into the CHL cell line (col. 11, lines 5 through col. 12, line 28).

It would have been obvious at the time the invention was made to practice the method of Kovoor by substituting SPA beads coated with WGA for the sepharose column to conduct the liquid scintillation assay since the SPA/WGA beads were commercially available and convenient to use in an old and routine assay method (*e.g.*, col. 5, lines 40-47). It further would have been obvious to transform a cell line with the a GPCR cDNA of Kovoor et al. as a source of GPCR-containing membranes in the assay instead of liposome membranes in order to better understand the association of GPCR with endogenous membrane-associated molecules and to a virtually endless supply of membranes from routinely cultured cells.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Krupnic et al. (Annu. Rev. Pharmacol. Toxicol., 38 :289,1998) describes the relationship of GPCRs, arrestins and kinases. Also listed are common G protein-coupled receptor kinase names, for example βARK (Table 1 on p. 293). Palczewski (Eur. J. Biochem., 248:261-269, 1997) describes the relationship of GPCRs to GRKs. Mundell et al.(Biochem., 38:8723-8732, 10 June 1999) describe transfection of HEK293-EBNA cells with one of several GPCRs: β_2AR, m2 and m3 muscarinic acetylcholine receptors (p. 8725, last two full paragraphs of col. 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

February 17, 2004